2-Dicyanomethylidene-3-ethoxymethylidene-2,3-dihydroindole in the synthesis of fused tri- and tetracyclic systems

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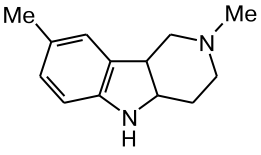
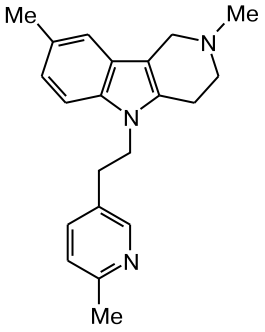
The reactions of 2-dicyanomethylidene-3-ethoxymethylidene-2,3-dihydroindole with hydrazine hydrate and phenylhydrazine afforded 2,3-diamino-4-cyanopyrido[4,3-*b*]indole and 3-amino-2-anilino-4-cyanopyrido[4,3-*b*]indole, respectively, and the reactions of the latter compounds with dimethylformamide diethyl acetal were studied. The reactions of 2,3-diamino-4-cyanopyrido[4,3-*b*]indole with benzaldehyde, ethyl acetoacetate, and acetylacetone were investigated. First representatives of new heterocyclic systems, *viz.*, [1,2,4]triazolo[1′,5′:1,6]pyrido[4,3-*b*]indole and pyrazolo[1′,5′:1,2]pyrido[4,3-*b*]indole, were synthesized. The structure of ethyl 6-cyano-5-[(*E*)-(dimethylamino)methylideneamino]-2-methyl-7*H*-pyrazolo[1′,5′:1,2]pyrido[4,3-*b*]indole-1-carboxylate was established by X-ray diffraction.

Key words: hydrazine hydrate, phenylhydrazine, pyrido[4,3-*b*]indoles (γ-carbolines), dimethylformamide diethyl acetal, amidines, heterocyclization, ethyl acetoacetate, benzaldehyde, acetylacetone, [1,2,4]triazolo[1′,5′:1,6]pyrido[4,3-*b*]indole, alkylation, pyrazolo[1′,5′:1,2]pyrido[4,3-*b*]indole, X-ray diffraction study.

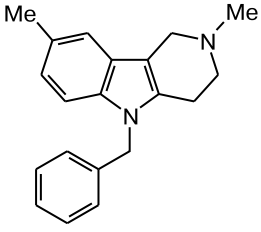
Compounds containing the pyrido[4,3-*b*]indole fragment have a broad spectrum of biological activities. Compounds of this class, for example, the neuroleptic agent Carbidinum (or Stobadine), the antihistaminic agents Dimebonum and Diazolinum (or Omeril), and the gastroenterological agent Alosetron (or Lotronex),[1,2] have found use as drugs. Substituted γ-carboline **1** is a selective $5HT_3$ serotonin receptor inhibitor.[3]



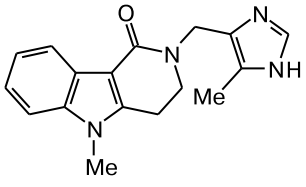
Carbidinum



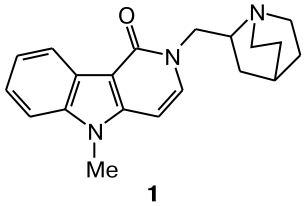
Dimebonum



Diazolinum



Alosetron



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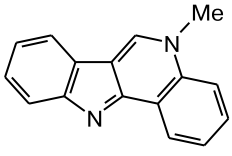
In this series of compounds, there are not only pharmacologically active compounds, but also chemotherapeutic agents. Thus the natural alkaloid isocryptolepine possesses strong antibacterial, antimalarial, and antitumor activities, which has provoked considerable interest in the synthesis of its analogs.[4—12]



Isocryptolepine

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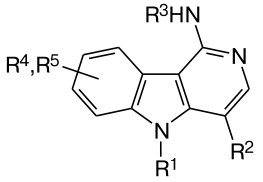
1-Amino-substituted pyrido[4,3-*b*]indoles **2** were shown to possess antitumor activity.[13] A series of substituted annulated γ-carboline derivatives **3** and **4** was synthesized.[14,15] Many of the latter compounds exhibit citotoxicity and possess antitumor activity. Compound **3** with $R^1 = H$, $R^2 = CH_2CH_2CH_2N(CH_3)_2$, and $R^3 = OH$ known as Intoplicine is an antitumor agent and a topoisomerase inhibitor.



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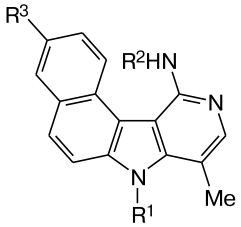

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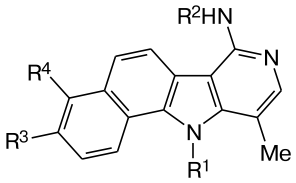

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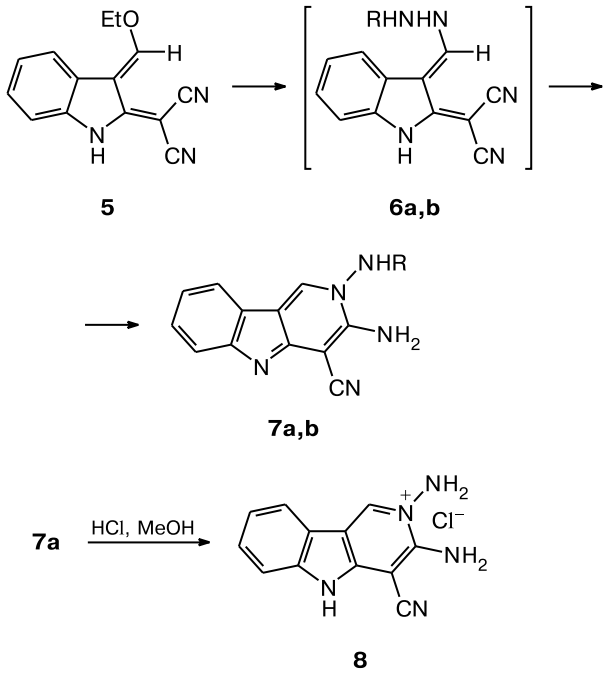
Thus, γ-carbolines are promising subjects for investigation of their biological activity. Hence, the synthesis of various derivatives of this series is topical and expedient.

Previously,[16] we have synthesized 2-dicyanomethylidene-3-ethoxymethylidene-2,3-dihydroindole (**5**) manifesting high reactivity toward nucleophilic agents.[17]

With the aim of synthesizing new γ-carboline derivatives and investigating their chemical and biological properties, in the present study we examined the reactions of compound **5** with hydrazine hydrate and phenylhydrazine.

It was found that the reaction of compound **5** with hydrazines does not stop at the step of formation of bicyclic derivatives **6a,b** and leads to the pyridine ring closure giving rise to substituted γ-carbolines **7a,b** (Scheme 1), as was observed in the reactions of compound **1** with some amines.[17] Thus the reaction of compound **5** with hydrazine hydrate ($pK_a = 8.07$) in isopropyl alcohol proceeds even at room temperature to give 2,3-diamino-4-cyanopyrido[4,3-*b*]indole (**7a**) in virtually quantitative yield (98%) in 1 h. The reaction of compound **5** with much less basic phenylhydrazine ($pK_a = 5.21$) in isopropyl alcohol does not proceed at room temperature, and 3-amino-2-anilino-4-cyanopyrido[4,3-*b*]indole (**7b**) could be obtained only upon refluxing. The ^{1}H NMR spectra of compounds **7a** and **7b** show signals for aromatic protons and protons in position 1 along with signals for two NH_2 groups (δ 6.36 (s) and 7.26 (br.s), 2 H each) for compound **7a** or signals for NH (δ 9.52 (br.s, 1 H)) and signals for NH_2 groups (δ 7.50 (br.s, 2 H)) for compound **7b**. Thus, the ^{1}H NMR spectra provide evidence that the reaction products have structures **7a**,**b** rather than the isomeric structures **6a**,**b**. For compound **7a**, its monohydrochloride **8** was obtained. The ^{1}H NMR spectrum of compound **8** shows signals for two NH_2 groups (δ 6.91 ($N(3)H_2$) and 8.54 ($N(2)H_2$), both br.s, 2 H each) along with a broadened signal for the indole proton at δ 12.84.

Scheme 1



R = H (**a**), Ph (**b**)

Reagents and conditions: for **7a**: $NH_2NH_2 \cdot H_2O$, Pr^iOH; for **7b**: NH_2NHPh, Pr^iOH, Δ.

It should be noted that the protonation of compound **7a** occurs at one nitrogen atom in position 2. This is attributed to the formation of the energetically favorable aromatic cation of salt **8**.

Due to the presence of two amino groups in the adjacent positions (2 and 3), diamines **7a,b** have considerable promise in the synthesis of tetracyclic systems containing the pyrido[4,3-*b*]indole fragment. The synthesis of polyheterocycles having a planar structure and containing a basic center are of particular interest, because compounds of this class can act as intercalators[2] and, after certain modifications, can exhibit antiviral and (or) antitumor activity.

Amide acetals are widely used in the synthesis of various heterocyclic compounds.[18] In this connection, we studied the reactions of diamines **7a,b** with dimethylformamide diethyl acetal (**9**). Refluxing of **7a** in dry toluene with an excess of acetal **9** results in the triazole ring closure giving rise to compound **10a**. The latter is a represen-

tative of a new heterocyclic system, *viz.*, [1,2,4]triazolo-[1′,5′:1,6]pyrido[4,3-*b*]indole, which can exist in three tautomeric forms (**A**, **B**, and **C**) (Scheme 2).

To elucidate the scheme of formation of tetracyclic compound **10a**, we made an attempt to prepare intermediates. However, no reaction occurred even upon prolonged storage (5 days) of diamine **7a** in an excess of acetal **9** in the presence of a catalytic amount of pyrrolidine (TLC data), and product **10a** formed only upon heating.

The reaction of compound **7b** with an excess of acetal **9** in dry toluene gave amidine **11**, whereas the triazole ring closure (as in the case of diamine **7a**) did not occur.

The storage of compound **11** in saturated methanolic ammonia at room temperature resulted in transamination giving rise to compound **12** rather than in the cyclization to tetracyclic compound **13**. The IR spectrum of the reaction product contains an absorption band at 2218 cm^{-1} (C≡N group) and a broad band at 3250 cm^{-1} (NH_2 group). The ^1H NMR spectrum contains a signal for the proton of the N=CH group at δ 8.73 (t, 1 H).

Then we studied the condensation of diamine **7a** with carbonyl compounds, such as benzaldehyde, ethyl acetoacetate, and acetylacetone.

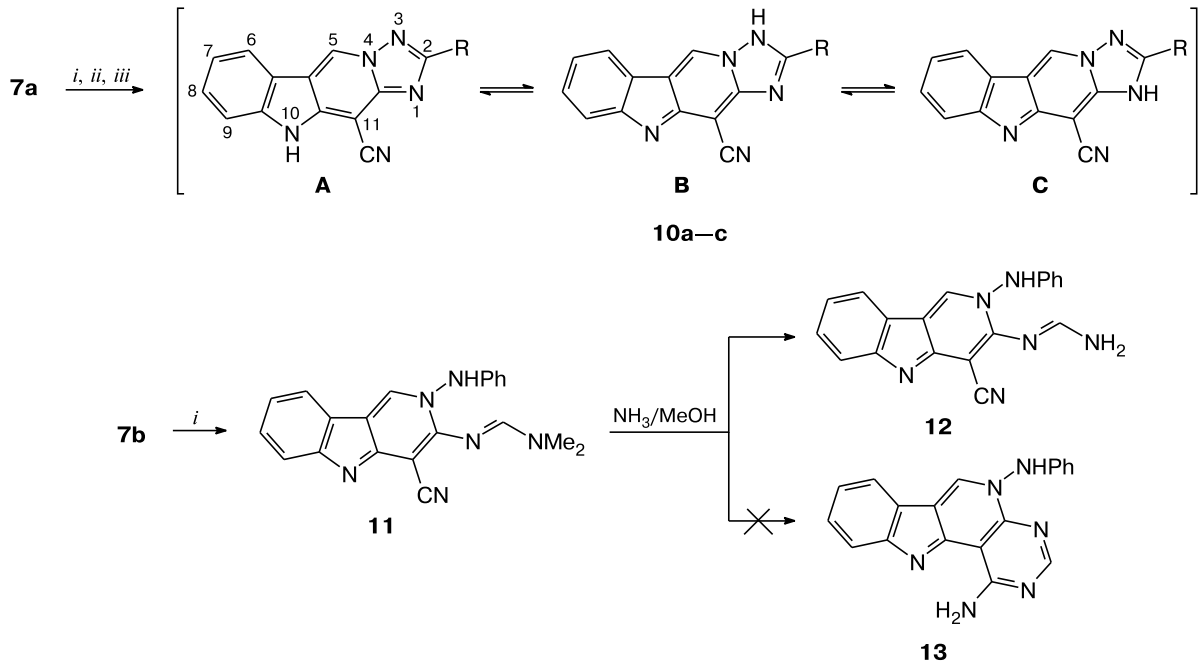
Refluxing of diamine **7a** with benzaldehyde in dry toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate afforded triazolopyridoindole **10b** in good yield (73%).

The reaction of diamine **7a** with ethyl acetoacetate under reflux in propan-2-ol proceeds differently and very unexpectedly. Thus we isolated compound **14**, which is the first representative of a new heterocyclic system, *viz.*, pyrazolo[1′,5′:1,2]pyrido[4,3-*b*]indole (Scheme 3). The IR spectrum of compound **14** shows absorption bands of C=O (1683 cm^{-1}) and CN (2212 cm^{-1}) groups and intense absorption bands at 3295 and 3414 cm^{-1} assigned to NH_2 and NH vibrations, respectively. The ^1H NMR spectrum of compound **14**: δ 1.38 (t, 3 H, $COCH_2C\underline{H}_3$, J = = 7.5 Hz); 2.58 (s, 3 H, CH_3); 4.42 (q, 2 H, $COC\underline{H}_2CH_3$, J = 7.5 Hz); 7.12 and 7.21 (both t, 1 H each), 7.49 and 7.89 (both d, 1 H each) (H(8)—H(11)); 7.79 (s, 2 H, NH_2); 12.02 (br.s, 1 H, NH). Apparently, the condensation of ethyl acetoacetate involves the amino group in the pyridine ring in position 2 to form the imino intermediate **A**. The latter is transformed into aminocrotonate **B**, which is typical of the reactions of ethyl acetoacetate with amines. Aminocrotonate **B** undergoes cyclization to the dihydropyrazole derivative **D**, which is oxidized into energetically favorable aromatic tetracyclic compound **14** under the reaction conditions (see Scheme 3).

To confirm the presence of the primary amino group in position 5, we performed the reaction of compound **14** with acetal **9** giving rise to the corresponding amidine **15**.

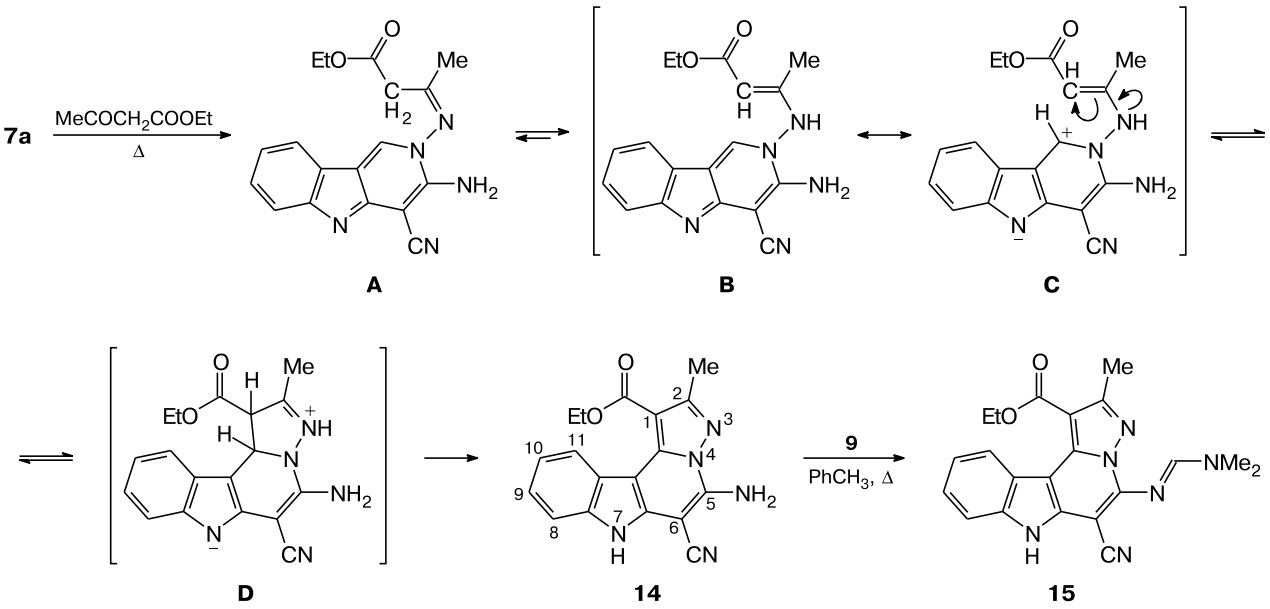
We obtained crystals of compound **15**, and the structure of this compound was established by X-ray diffraction (Fig. 1). All geometric parameters of molecule **15** have

Scheme 2



Reagents and conditions: *i*. for **10a** and **11**: $(EtO)_2CHNMe_2$ (**9**), toluene, Δ; *ii*. for **10b**: PhCHO, *p*-toluenesulfonic acid · H_2O, toluene, Δ; *iii*. for **10c**: $AcCH_2Ac$, Pr^iOH, Δ or AcOH, Δ.

Scheme 3



values similar to the corresponding parameters found in the Cambridge Structural Database.[19] In the crystals, the cyano and amino groups are involved in intermolecular hydrogen bonds (Table 1), through which the molecules are linked into centrosymmetric dimers.

In connection with the unexpected formation of tetracyclic compound **14** in the reaction of **7a** with ethyl acetoacetate, we studied the analogous reaction with another dicarbonyl compound, *viz.*, acetylacetone. The reaction of compound **7a** with acetylacetone in dry toluene afforded a mixture of two compounds (TLC data), but only product **10c** was isolated in the individual state (recrystallization of the reaction mixture from 67% aqueous DMF) (see Scheme 2). However, the mass spectrum of the crude product contains molecular ion peaks of the major compound (248 $[247 + H]^+$, 270 $[247 + Na]^+$, 495 $[2\times247 + H]^+$) along with a molecular ion peak at 304 $[303 + H]^+$, which can be assigned to product **16** that is formed analogously to compound **14** (Scheme 4). The ^{1}H NMR spectrum of

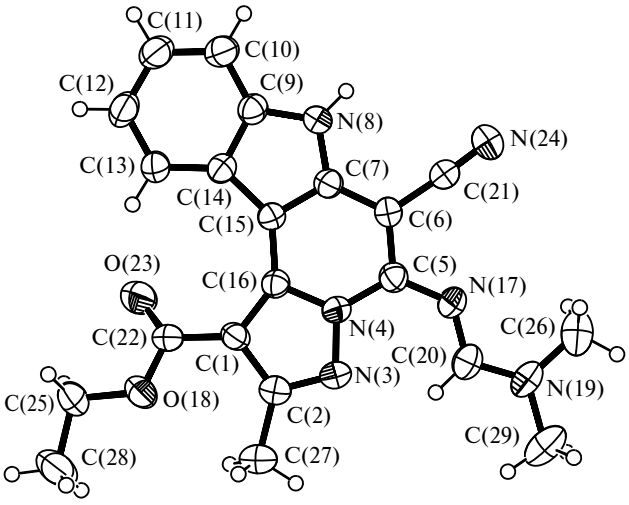
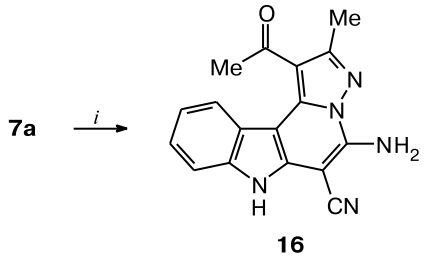


Fig. 1. Molecular structure of **15**. Nonhydrogen atoms are represented by displacement ellipsoids at the 50% probability level.

Scheme 4



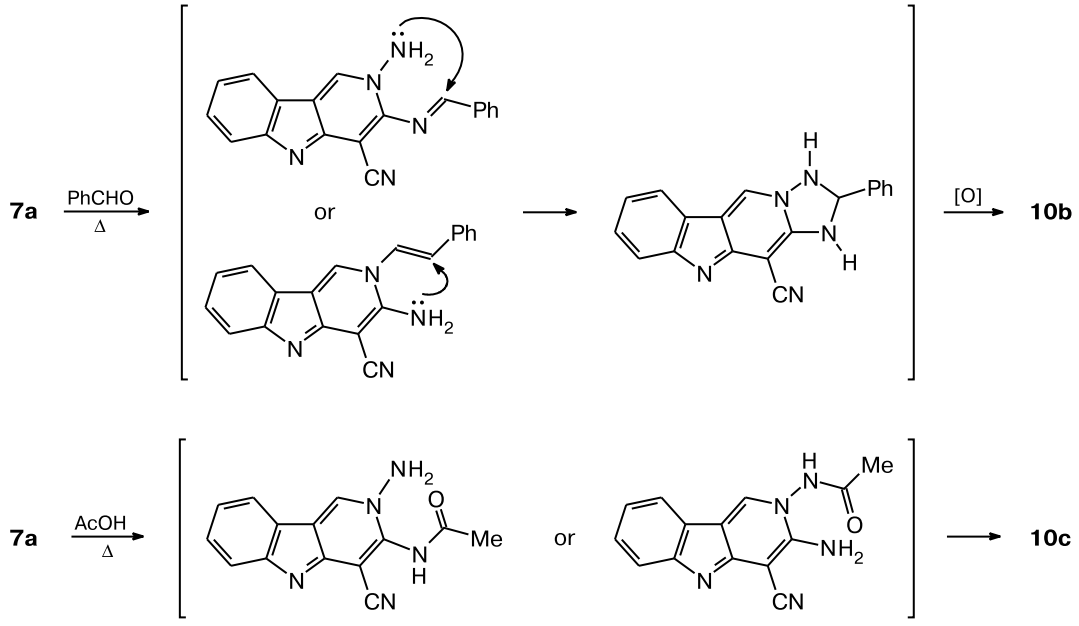
i. $AcCH_2Ac$, toluene.

Table 1. Geometric parameters of the hydrogen bonds in the structure of **15**

Parameter	Value
Bond	*d*/Å
N(8)—H(8)	0.86
H(8)...N(24)	2.10
N(8)...N(24)	2.938(5)
Angle	ω/deg
N(8)—H(8)...N(24)	166

Note. Symmetry code: N(8)—H(8)...N(24), $1 - x$, $2 - y$, $1 - z$.

Scheme 5



the crude product shows signals for protons of compound **10c** along with signals that can be assigned to protons of compound **16**: 2.60 and 2.62 (both s, 1 H each, 2 Me); 7.12—7.27 (m, 4 H, H(6)—H(9); 7.82 (s, 2 H, NH_2); 12.04 (br.s, 1 H, NH).

Compound **10c** was prepared also under other conditions, *viz.*, by refluxing compound **7a** in acetic acid. Samples of compound **10c** isolated in different experiments are identical in the spectroscopic and physical data.

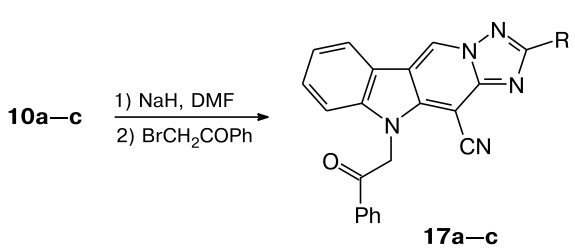
It can be suggested that in this case the reactions of **7a** with benzaldehyde and acetic acid proceed according to Scheme 5.

The alkylation of compounds **10a—c** with phenacyl bromide in dry DMF in an argon atmosphere in the presence of sodium hydride affords the corresponding derivatives **17a—c** in good yields (Scheme 6). The structures of the resulting N-substituted tetracyclic compounds were confirmed based on the NOEDIFF spectrum of compound **17a**. After the saturation of the signal for the methylene group (δ 6.33), the NOEDIFF spectrum contains signals for the protons of the phenyl group (δ 7.74, 8.18, both d, 2 H each) and a doublet for the proton in position 9 (δ 7.74, d, 1 H).

It should be noted that the ^{1}H NMR spectra of compounds **10a—c** and **17a—c** contain signals for the protons H(5) at δ 10.01—10.24. Such a substantial downfield shift of these signals is apparently attributed to the strong electron-withdrawing effect of the annulated triazole ring.

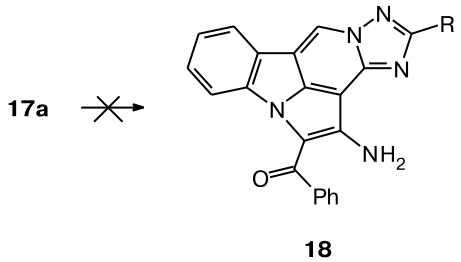
Attempts to prepare fused γ-carboline **18** by the Thorpe—Ziegler cyclization of compound **17a** failed (Scheme 7). After the prolonged reflux of compound **17a** with potassium *tert*-butoxide in *tert*-butanol, with sodium ethoxide in anhydrous ethanol, and with potassium *tert*-butoxide in pyridine, only the starting compound was isolated (in 45, 67, and 85% yields, respectively). Apparently, the Thor-

Scheme 6



R = H (**a**), R = Ph (**b**), R = Me (**c**)

Scheme 7



Reagents and conditions: Bu^{t}OH, Bu^{t}OK, refluxing; EtOH, EtONa, refluxing; Bu^{t}OK, pyridine.

pe—Ziegler cyclization of these γ-carbolines is hindered due to the formation of tetracyclic system **18** containing two fused five-membered rings. An unsuccessful attempt to perform cyclization under analogous conditions has been described previously[17,20] for the five-membered ring.

To sum up, we performed a series of transformations of 2-dicyanomethylidene-3-ethoxymethylidene-2,3-dihydroindole and synthesized pyrido[4,3-*b*]indole derivatives and the first representatives of new fused tetracyclic systems, *viz.*, [1,2,4]triazolo[1′,5′:1,6]pyrido[4,3-*b*]indole and pyrazolo[1′,5′:1,2]pyrido[4,3-*b*]indole.

Experimental

The ^{1}H NMR spectra were recorded on Bruker AC-300 and Bruker DRX-500 spectrometers in a DMSO-d_6 + CCl_4 mixture. The mass spectra were obtained on a Waters Micromass ZQ 2000 mass spectrometer in an ESI+ mode. The IR spectra were measured on a Perkin—Elmer 457 instrument in Nujol mulls. The melting points were determined on a Boetius hot-stage apparatus.

The yields, melting points, and the data from elemental analysis, mass spectrometry, and IR spectroscopy are given in Table 2.

2-Dicyanomethylidene-3-ethoxymethylidene-2,3-dihydroindole (5) was synthesized according to a procedure described previously.[17]

2,3-Diamino-4-cyanopyrido[4,3-*b*]indole (7a). A mixture of compound **5** (2.60 g, 11 mmol), hydrazine hydrate (3.84 g, 77 mmol), and propan-2-ol ((30 mL) was stirred at room temperature for 1 h. Then the reaction mixture was cooled to 0 °C. The precipitate was filtered off, washed with propan-2-ol and diethyl ether, and dried. Compound **7a** was obtained in a yield of 2.40 g. ^{1}H NMR, δ: 6.36 (s, 2 H, N(3)H_2); 6.96 (t), 7.26 (t), 7.38 (d), 7.85 (d) (all 1 H each, H(6)—H(9), J_0 = 7.5 Hz); 7.26 (br.s, 2 H, NH_2); 8.47 (s, 1 H, H(1)).

3-Amino-2-anilino-4-cyanopyrido[4,3-*b*]indole (7b). A mixture of compound **5** (0.60 g, 2.53 mmol), phenylhydrazine (0.55 g, 5.06 mmol), and propan-2-ol (7 mL) was stirred at room temperature for 1 h under argon. Then the reaction mixture was heated to reflux, stirred for 40 min, and cooled to 0 °C. The precipitate was filtered off, washed with propan-2-ol and diethyl ether, and dried. Compound **7b** was obtained in a yield of 0.68 g. ^{1}H NMR, δ: 6.62 (d, 2 H), 6.95 (m, 2 H), 7.26 (m, 3 H), 7.41 (d, 1 H), 7.86 (d, 1 H) (H(6)—H(9) Ph, J_0 = 7.5 Hz); 7.50 (br.s, 2 H, NH_2); 8.50 (s, 1 H, H(1)), 9.52 (br.s, 1 H, NH).

2,3-Diamino-4-cyanopyrido[4,3-*b*]indole hydrochloride (8). A mixture of compound **7a** (0.32 g, 1.44 mmol), concentrated hydrochloric acid (0.3 mL), and methanol (6 mL) was stirred at room temperature for 2 h. Then the reaction mixture was cooled to 0 °C. The precipitate was filtered off, washed with propan-2-ol and diethyl ether, and dried. Compound **8** was obtained in a yield of 0.19 g. ^{1}H NMR, δ: 6.91 (br.s, 2 H, N(3)H_2); 7.35 (t, 1 H), 7.55 (m, 2 H), 8.17 (d, 1 H) (H(6)—H(9), J_0 = 7.5 Hz); 8.54 (br.s, 2 H, N(2)H_2); 9.29 (s, 1 H, H(1)); 12.84 (br.s, 1 H, NH).

10*H*- (10aA), 3*H*- (10aB), or 1*H*-11-cyano[1,2,4]triazolo[1′,5′:1,6]pyrido[4,3-*b*]indole (10aC). A mixture of compound **7a** (2.52 g, 11 mmol), acetal **9** (2.06 mL, 1.77 g, 12 mmol), and dry toluene (25 mL) was refluxed for 2 h. Then more acetal (2.06 mL) was added, the reaction mixture was refluxed for 3 h, a new portion of the acetal (2.06 mL) was added, the mixture was refluxed for 2 h 30 min, and an additional portion of the acetal (1.03 mL, 0.89 g, 6 mmol) was added. Then the reaction mixture was refluxed for 2 h and cooled to 0 °C. The precipitate was filtered off, washed with propan-2-ol and diethyl ether, and dried. Compound **10a** was obtained in a yield of 2.36 g. ^{1}H NMR, δ: 7.31 (t, 1 H), 7.51 (m, 2 H), 8.24 (d, 1 H) (H(6)—H(9), J_0 = 7.5 Hz); 8.46 (s, 1 H, H(2)); 10.14 (s, 1 H, H(5)); 12.52 (br.s, 1 H, NH).

10*H*- (10bA), 3*H*- (10bB), or 1*H*-2-phenyl-11-cyano[1,2,4]triazolo[1′,5′:1,6]pyrido[4,3-*b*]indole (10bC). A mixture of compound **7a** (0.68 g, 3.05 mmol), benzaldehyde (0.93 mL, 0.97 g, 9.15 mmol), *p*-toluenesulfonic acid monohydrate (0.05 g, 0.26 mmol), and dry toluene (7 mL) was refluxed for 8 h 30 min. Then more benzaldehyde (0.50 mL, 0.52 g, 4.9 mmol) was added. The reaction mixture was refluxed additionally for 7 h, kept at room temperature for 15 h, refluxed for 4 h, and cooled to 0 °C. The precipitate was filtered off, washed with propan-2-ol and diethyl ether, and dried. Compound **10b** was obtained in a yield of 0.69 g. ^{1}H NMR, δ: 7.34 (t, 1 H), 7.54 (m, 5 H), 8.26 (m, 3 H) (H(6)—H(9), Ph, J_0 = 7.5 Hz); 10.08 (s, 1 H, H(5)); 12.53 (br.s, 1 H, NH).

2-Anilino-4-cyano-3-dimethylaminomethylideneaminopyrido[4,3-*b*]indole (11). A mixture of compound **7b** (0.42 g, 1.41 mmol), acetal **5** (0.36 mL, 0.31 g, 2.11 mmol), and dry toluene (5 mL) was refluxed for 1 h 30 min. More acetal (0.15 mL) was added, and the reaction mixture was refluxed for 1 h and cooled to 0 °C. The precipitate was filtered off, washed with propan-2-ol and diethyl ether, and dried. Compound **11** was obtained in a yield of 0.23 g. ^{1}H NMR, δ: 3.39 (s, 6 H, N(CH_3)$_2$); 7.04 (m, 2 H), 7.36 (m, 3 H), 7.57 (t, 2 H), 7.95 (d, 2 H) (H(6)—H(9), Ph, J_0 = = 7.5 Hz); 8.70 (s, 1 H, N=CH); 9.23 (s, 1 H, H(1)); 11.37 (s, 1 H, NH)).

3-Aminomethylideneamino-2-anilino-4-cyanopyrido[4,3-*b*]indole (12). A mixture of compound **11** (0.36 g, 1.02 mmol) and saturated methanolic ammonia (10 mL) was kept at room temperature for 45 h. The precipitate was filtered off and washed with diethyl ether. Compound **12** was obtained in a yield of 0.18 g. ^{1}H NMR, δ:* 7.03 (t, 1 H), 7.12 (t, 1 H), 7.39 (m, 2 H), 7.57 (t, 2 H), 7.85 (d, 1 H), 7.95 (d, 2 H) (H(6)—H(9), Ph, J_0 = 7.5 Hz); 8.73 (t, 1 H, N=CH, J_0 = 11.6 Hz), 9.26 (s, 1 H, H(1)), 11.31 (br.s, 1 H, NH)).

Ethyl 5-amino-6-cyano-2-methyl-7*H*-pyrazolo[1′,5′:1,2]pyrido[4,3-*b*]indole-1-carboxylate (14). A mixture of compound **7a** (1.35 g, 6.05 mmol), ethyl acetoacetate (0.78 mL, 0.80 g, 6.12 mmol), and propan-2-ol (20 mL) was refluxed for 6 h 30 min and kept at room temperature for 15 h. Then more ethyl acetoacetate (0.78 mL) was added, the reaction mixture was refluxed for 7 h and kept at room temperature for 15 h, and a new portion of ethyl acetoacetate (0.78 mL) was added. The reaction mixture was refluxed for 2 h and cooled to 0 °C. The precipitate was filtered off, washed with propan-2-ol and diethyl ether, and dried. Compound **14** was obtained in a yield of 1.15 g.

Ethyl 6-cyano-5-[(*E*)-(dimethylamino)methylideneamino]-2-methyl-7*H*-pyrazolo[1′,5′:1,2]pyrido[4,3-*b*]indole-1-carboxylate (15). A mixture of compound **14** (0.77 g, 2.31 mmol), acetal **9** (0.43 mL, 0.37 g, 2.54 mmol), and dry toluene (15 mL) was refluxed for 1 h 30 min. Then a new portion of the acetal (0.43 mL) was added, and the reaction mixture was refluxed for

* The chemical shifts of the signals for the NH_2 group overlap with those of the signals for H(6)—H(9) and Ph.

Table 2. Yields, melting points, data from elemental analysis, mass spectrometry, and IR spectroscopy for compounds **7a,b**, **8**, **10a—c**, **11**, **12**, **14, 15**, and **17a—c**

Compound	Yield (%)	M.p. /°C	Solvent	Found / Calculated (%)			Molecular formula	MS, *m/z*	IR, ν_{max}/cm^{-1}	
				C	H	N			C≡N (C=O)	NH, NH_2
7a	98	250 (with decomp.)	50% aqueous DMF	63.91 64.56	4.35 4.06	31.51 31.98	$C_{12}H_9N_5$	224 $[M + H]^+$, 447 $[2 M + H]^+$	2209	3175, 3316, 3362
7b[a]	90	260—263	DMF : Pr^iOH, 1 : 3	67.56 67.64	5.31 5.43	22.44 22.63	$C_{21}H_{20}N_6O$	300 $[M + H]^+$, 322 $[M + Na]^+$, 599 $[2 M + H]^+$	2118	3206, 3308, 3392
8	51	284—285	90% aqueous Pr^iOH	—	—	—	$C_{12}H_{10}N_5Cl$[b]	208 $[M + H - NH_2]^+$, 224 $[M + H]^+$, 447 $[2M + H]^+$	2228	3248, 3362
10a	92	>350	75% aqueous DMF	67.20 66.94	3.60 3.03	29.98 30.03	$C_{13}H_7N_5$	234 $[M + H]^+$, 256 $[M + Na]^+$, 272 $[M + K]^+$, 467 $[2 M + H]^+$, 489 $[2 M + Na]^+$	2220	3115 (br.)
10b	73	>350	60% aqueous DMF	73.90 73.77	3.58 3.59	22.96 22.64	$C_{19}H_{11}N_5$	310 $[M + H]^+$, 619 $[2M + H]^+$	2222	3200 (br.)
10c	***A*** 32 ***B*** 30	>350	67% aqueous DMF	68.58 68.00	3.64 3.67	28.09 28.33	$C_{14}H_9N_5$	248 $[M + H]^+$, 270 $[M + Na]^+$, 495 $[2M + H]^+$	2224	3252
11	46	180—182	Pr^iOH	71.57 71.17	5.16 5.12	23.35 23.72	$C_{21}H_{18}N_6$	310 $[M + H - NMe_2]^+$, 355 $[M + H]^+$, 709 $[2M + H]^+$	2170	3200 (br.)
12	54	229—231	67% aqueous DMF	69.37 69.92	4.17 4.32	26.21 25.75	$C_{19}H_{14}N_6$	327 $[M + H]^+$, 349 $[M + Na]^+$, 365 $[M + K]^+$, 653 $[2 M + H]^+$, 675 $[2 M + Na]^+$	2218	3250, 3493
14	57	219—220	Pr^iOH	64.51 64.85	4.54 4.54	21.30 21.01	$C_{18}H_{15}N_5O_2$	334 $[M + H]^+$, 667 $[2M + H]^+$, 689 $[2 M + Na]^+$, 1000 $[3M + H]^+$	2212 (1683)	3295, 3414
15	89	295—297	DMF	64.85 64.93	5.06 5.19	21.84 21.64	$C_{21}H_{20}N_6O_2$	389 $[M + H]^+$, 411 $[M + Na]^+$, 777 $[2M + H]^+$, 1165 $[3M + H]^+$	2222 (1697)	3256
17a	90	318—321	67% aqueous DMF	71.80 71.78	3.66 3.73	20.15 19.94	$C_{21}H_{13}N_5O$	352 $[M + H]^+$, 374 $[M + Na]^+$, 703 $[2 M + H]^+$, 725 $[2 M + Na]^+$	2218 (1692)	—
17b	53	>350	80% aqueous DMF	75.91 75.86	3.94 4.01	16.57 16.39	$C_{27}H_{17}N_5O$	428 $[M + H]^+$, 450 $[M + Na]^+$, 855 $[2 M + H]^+$, 877 $[2 M + Na]^+$, 1282 $[3 M + H]^+$	2214 (1691)	—
17c	45	325	80% aqueous DMF	72.40 72.31	3.95 4.14	19.36 19.17	$C_{22}H_{15}N_5O$	366 $[M + H]^+$, 388 $[M + Na]^+$, 731 $[2 M + H]^+$, 753 $[2 M + Na]^+$	2216 (1645)	—

[a] The ^1H NMR spectrum of compound **7b** shows signals for one molecule of DMF (δ): 7.92 (s, 1 H, CH); 3.20 and 2.50 (both s, 1 H each, NMe_2).

[b] Found (%): Cl, 13.20. Calculated (%): Cl, 13.20.

4 h and cooled to 0 °C. The precipitate was filtered off, washed with propan-2-ol and diethyl ether, and dried. Compound **15** was obtained in a yield of 0.8 g. ^{1}H NMR, δ: 1.31 (t, 3 H, $CH_2C\underline{H}_3$); 4.37 (q, 2 H, $C\underline{H}_2CH_3$); 2.46 (s, 3 H, CH_3); 3.15 and 3.20 (both s, 3 H each, $N(CH_3)_2$); 7.13 (t), 7.23 (t), 7.50 (d), 7.81 (d) (1 H each, H(8)—H(11), J_0 = 7.5 Hz); 8.84 (s, 1 H, N=CH).

10*H*- (10cA), 3*H*- (10cB), or 1*H*-2-methyl-11-cyano[1,2,4]triazolo[1′,5′:1,6]pyrido[4,3-*b*]indole (10cC) and 1-acetyl-5-amino-6-cyano-2-methyl-7*H*-pyrazolo[1′,5′:1,2]pyrido[4,3-*b*]indole (16). ***A.*** A mixture of compound **7a** (0.8 g, 3.59 mmol), acetylacetone (0.41 mL, 0.39 g, 3.59 mmol), and propan-2-ol (10 mL) was refluxed for 1 h. Then more acetylacetone (0.41 mL) was added, and the reaction mixture was refluxed for 2 h, kept at room temperature for 15 h, refluxed for 2 h, and cooled to 0 °C. The precipitate was filtered off, washed with propan-2-ol and diethyl ether, and dried. A mixture of compounds **10c** and **16** was obtained in a yield of 0.54 g. The recrystallization of this mixture (0.25 g) from 67% aqueous DMF afforded compound **10c** in a yield of 0.08 g.

B. A mixture of compound **7a** (0.30 g, 1.35 mmol) and acetic acid (3 mL) was refluxed for 2 h, kept at room temperature for 15 h, refluxed for additional 7 h, and cooled to 0 °C. The precipitate was filtered off, washed with propan-2-ol and diethyl ether, and dried. Compound **10c** was obtained in a yield of 0.1 g. ^{1}H NMR, δ: 2.50 (s, 3 H, CH_3); 7.34 (t, 1 H), 7.52 (m, 2 H), 8.25 (d, 1 H) (H(6)—H(9), J_0 = 7.5 Hz); 10.01 (s, 1 H, H(5)); 12.52 (br.s, 1 H, NH).

10-Benzoylmethyl-11-cyano[1,2,4]triazolo[1′,5′:1,6]pyrido[4,3-*b*]indole (17a). Sodium hydride (0.82 g, 21 mmol) as a 60% suspension in Vaseline oil was added portionwise to a solution of compound **10a** (3.32 g, 14 mmol) in dry DMF (25 mL) under argon. The reaction mixture was stirred for 2 h and phenacyl bromide (4.18 g, 20 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, kept at room temperature for 15 h, and cooled to 0 °C. The precipitate was filtered off, washed with propan-2-ol and diethyl ether, and dried. Compound **17a** was obtained in a yield of 2.35 g. ^{1}H NMR, δ: 6.33 (s, 2 H, $C\underline{H}_2$Ph); 7.34—7.75 (m, 6 H), 8.18 (d, 2 H), 8.34 (d, 1 H) (H(6)—H(9), Ph, J_0 = 7.5 Hz); 8.44 (s, 1 H, H(2)); 10.24 (s, 1 H, H(5)).

10-Benzoylmethyl-11-cyano-2-phenyl[1,2,4]triazolo[1′,5′:1,6]pyrido[4,3-*b*]indole (17b). Sodium hydride (0.08 g, 2.18 mmol) as a 60% suspension in Vaseline oil was added portionwise to a solution of compound **10b** (0.45 g, 1.46 mmol) in dry DMF (6 mL) under argon. The reaction mixture was stirred for 40 min and phenacyl bromide (0.43 g, 2.18 mmol) was added. The reaction mixture was stirred at room temperature for 6 h, kept at room temperature for 15 h, and cooled to 0 °C. The precipitate was filtered off, washed with propan-2-ol and diethyl ether, and dried. Compound **17b** was obtained in a yield of 0.33 g. ^{1}H NMR, δ: 6.33 (s, 2 H, $C\underline{H}_2$Ph); 7.37—7.76 (m, 9 H), 8.19 (d, 2 H), 8.26 (d, 2 H), 8.34 (d, 1 H) (H(6)—H(9), $CH_2\underline{Ph}$, Ph, J_0 = 7.5 Hz); 10.22 (s, 1 H, H(5)).

10-Benzoylmethyl-11-cyano-2-methyl[1,2,4]triazolo[1′,5′:1,6]pyrido[4,3-*b*]indole (17c). Sodium hydride (0.11 g, 2.91 mmol) as a 60% suspension in Vaseline oil was added portionwise to a solution of compound **10c** (0.48 g, 1.94 mmol) in dry DMF ((5 mL) under argon. The reaction mixture was stirred for 40 min and phenacyl bromide (0.48 g, 2.91 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, kept at room temperature for 15 h, and cooled to 0 °C. The precipitate was filtered off, washed with ipropan-2-ol and diethyl ether, and dried. Compound **17c** was obtained in a yield of 0.32 g. ^{1}H NMR, δ: 2.50 (s, 3 H, CH_3); 6.30 (s, 2 H, $C\underline{H}_2$Ph); 7.30—7.88 (m, 6 H), 8.17 (d, 2 H), 8.32 (d, 1 H) (H(6)—H(9), Ph, J_0 = 7.5); 10.08 (s, 1 H, H(5)).

Table 3. Crystallographic data for compound **15**

Parameter	Characteristics
Molecular formula	$C_{21}H_{20}N_6O_2$
Crystal system	Моноклинная
Space group	$P2_1/c$
Unit cell parameters	
a/Å	7.4365(12)
b/Å	9.474(3)
c/Å	27.474(5)
β/deg	92.132(15)
V/Å^3	1953.4(8)
Z	4
d_{calc} (g cm^{-3})	1.321
μ/mm^{-1}	0.726
Radiation	CuKα
θ_{max}	69.93°
Number of independent reflections	3561
$R(F)$	0.0626
$R_w(F^2)$	0.1902
GOOF	1.01

X-ray diffraction study. The crystal structure of **15** was established by X-ray diffraction. The X-ray diffraction data were collected on a single-crystal four-circle CAD-4 diffractometer (CuKα radiation, graphite monochromator) at room temperature. The structure was solved by direct methods with the use of the SHELXS97 program package[21] and refined with anisotropic displacement parameters for nonhydrogen atoms using the SHELXL97 program package.[21] The hydrogen atoms were positioned geometrically and refined using a riding model. The crystal structure of **15** was deposited with the Cambridge Crystallographic Data Centre;[19] the CCDC reference number is 714418. Principal crystallographic parameters are given in Table 3. The geometric parameters of the hydrogen bonds are listed in Table 1.

References

1. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Drugs*], Torgsin, Kharkov, 1998, **2**, 1235 pp. (in Russian).
2. V. G. Granik, *Lekarstva: Farmakologicheskii, biokhimicheskii i khimicheskii aspekty* [*Drugs. Pharmacological, Biochemical, and Chemical Aspects*], Vuzovskaya kniga, Moscow, 2001, 407 pp. (in Russian).
3. R. D. Clark, A. B. Miller, J. Berger, D. B. Repke, K. K. Weinhardt, B. A. Kowalczyk, R. M. Eglen, D. W. Bonhaus, Ch.-H. Lee, A. D. Miche1, W. L. Smith, E. H. F. Wongll, *J. Med. Chem.,* 1993, **36**, 2645.
4. S. V. Dubovitskii, O. S. Radchenko, V. L. Novikov, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 2797 [*Russ. Chem. Bull.* (*Engl. Transl.*), 1996, **45**, 2656].
5. R. N. Kumar, T. Suresh, P. S. Mohan, *Tetrahedron Lett.*, 2002, **43**, 3327.

6. T. H. M. Jonckers, B. U. W. Maes, G. L. F. Lemiиre, G. Rombouts, L. Pieters, A. Haemers, R. A. Dommisse, *Synlett*, 2003, **5**, 615.
7. L. He, H.-X. Chang, T. Ch. Chou, N. Savaraj, C. C. Cheng, *Eur. J. Med. Chem.*, 2003, **38**, 101.
8. P. Molina, M. Alajarin, A. Vidal, *Tetrahedron*, **46**, 1063.
9. S. Cacchi, G. Fabrizi, P. Pace, F. Marinelli, *Synlett,* 1999, No. 5, 620.
10. A. Mouaddib, B. Joseph, A. Hasnaoui, J.-Y. Méroura, *Synthesis*, 2000, 549.
11. J. Bergman, R. Engqvist, C. Stalhandske, H. Wallberg, *Tetrahedron*, 2003, **59**, 1033.
12. H. Li, H. Yang, J. L. Petersen, K. K. Wang, *J. Org. Chem.*, 2004, **69**, 4500.
13. E. Bisagni, C. H. Nguyen, A. Pierr, O. Popin, P. Cointet, P. Grosl, *J. Med. Chem.*, 1988, **31**, 398.
14. C. H. Nguyen, J.-M. Lhoste, F. Lavelle, M.-C. Bissery, E. Bisagni, *J. Med. Chem.*, 1990, **33**, 1519.
15. P.-J. Aragon, A.-D. Yapi, F. Pinguet, J.-M. Chezal, J.-C. Teulade, J.-P. Chapat, Y. Blanche, *Chem. Pharm. Bull.*, 2004, **52**, 659.
16. T. V. Golovko, N. P. Solov´eva, O. S. Anisimova, O. B. Smirnova, M. I. Evstratova, S. S. Kiselev, V. G. Granik, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 171 [*Russ. Chem. Bull., Int. Ed.*, 2008, **57**, 177].
17. O. B. Smirnova, T. V. Golovko, L. M. Alekseeva, A. S. Shashkov, V. G. Granik, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 2361 [*Russ. Chem. Bull., Int. Ed.*, 2008, **57**, 2410].
18. V. G. Granik, *Atsetali amidov i laktamov* [*Acetals of Amides and Lactams*], Vuzovskaya kniga, Moscow, 2008 (in Russian).
19. F. H. Allen, *Acta Crystallogr., Sect. B*, 2002, **58**, 380.
20. N. I. Smetskaya, Ph. D. (Chem.) Thesis, Novokuznetsk Scientific Research Chemical Pharmaceutical Institute, 1985, 142 pp. (in Russian)
21. G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 2008, **64**, 112.

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